TABLE 1.—*Causes of Neurogenic Diabetes Insipidus in the Neonatal Period*

Intracranial defects
Holoprosencephaly
Septo-optic dysplasia
Infections
Listerial sepsis
Meningitis—streptococcal
Meningococcal septicemia
Intracranial tumors
Trauma
Intraventricular hemorrhage
Brain death

of 121 nmol per liter (4.4 μg per dl [normal, 110 to 520 nmol per liter]), thyroid-stimulating hormone level of 3.9 mU per liter, an unenhanced brain computed tomographic scan showing no intracranial defects, normal optic nerves and septum pellucidum, and normal plain films of the skull and long bones.

The infant had complete resolution of vomiting and lethargy, and the findings of a physical examination on discharge were completely within normal limits. She was feeding well on formula and was sent home on a regimen of intranasal desmopressin. At 12 weeks of age she was noted to have poor response to visual stimuli. An ophthalmologic examination revealed nystagmus and hypoplastic optic nerves—approximately 10% normal size. The diagnosis of de Morsier's syndrome (septo-optic dysplasia) was made.

Discussion

Neurogenic diabetes insipidus of neonates usually presents in a patient with known predisposing risk factors (Table 1). As such, the neonate is typically being treated or followed for the preexisting conditions, and diabetes insipidus is discovered because of abnormal laboratory values or urine output. The patient we describe presented with diabetes insipidus at 21 days of age with no known predisposing conditions, and an initial workup proved uninformative regarding a cause. Of interest is that the baby reportedly preferred water over formula since birth, although previous physical examinations revealed no signs of dehydration. Additionally, eye movements and gross visual responses were noted to be normal in the newborn nursery. A further evaluation at 3 months of age revealed diminished visual responses and findings consistent with de Morsier's syndrome (septo-optic dysplasia).

The de Morsier's syndrome is caused by congenital midline brain malformations thought to occur at 6 to 8 weeks of gestational age and involves cerebral structures, optic nerves, pituitary gland, and the hypothalamus to a variable degree. It usually affects the offspring of young primigravid mothers (which was the case in this patient). Unlike the patient described here, infants with de Morsier's syndrome usually present with ophthalmologic abnormalities as the chief parental concern.[5] The endocrine abnormalities are found subsequently and can be multiple or isolated, although growth hormone deficiency is the most consistent abnormality. Approximately 40% of patients will have an absence of the septum pellucidum, although its presence or absence does not correlate with endocrine abnormalities.[6] Again, the patient we described had a normal septum pellucidum.

This case exemplifies the need for continued follow-up to determine the cause of central diabetes insipidus in an infant once the diagnosis has been made. Greger and co-workers reported that in a series of 58 children, the cause of diabetes insipidus could eventually be found in more than 90% of patients.[7] An ongoing evaluation of patients with diabetes insipidus in whom no obvious cause is evident should include a computed tomographic scan of the brain at intervals, repeated evaluations of the hypothalamic-pituitary axis, and astute physical examinations.

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Occult Retroperitoneal Carcinoid Tumor With Flushing and Solitary Lung Metastasis

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FLUSHING IS the hallmark symptom of the carcinoid syndrome, occurring in 63% to 96% of affected patients.[1-4] By the time of overt symptoms, patients with carcinoid syndrome usually have liver metastases and pronounced elevations in urinary 5-hydroxyindoleacetic acid (5-HIAA), and the diagnosis is straightforward. We describe the diagnostic challenge of a patient with flushing who had initially normal to minimally elevated urinary 5-HIAA levels and a small pulmonary nodule and later was shown to have an occult metastatic carcinoid tumor of apparent retroperitoneal origin. His dramatic response to the long-acting somatostatin analogue, compound SMS-201-995 (octreotide [Sandostatin, Sandoz Research Institute, East Hanover, NJ]), with relief of subsequent intractable abdominal pain is also reported.

Report of a Case

The patient, a 58-year-old man, had mild facial flushing and intermittently loose stools in April 1985. That fall, his internist measured 24-hour urinary 5-HIAA concentrations on three occasions, with values of 40, 43, and 60 μmol per day (normal 10 to 52), and abdominal computed tomography

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ABBREVIATIONS USED IN TEXT
CT = computed tomography
5-HIAA = 5-hydroxyindoleacetic acid

(CT) showed mild retrocrural and periaortic adenopathy with no evidence of liver metastasis. His initial chest x-ray film was normal. A urinary histamine level was slightly elevated at 75 μg per 24 hours (normal 17 to 68), but a bone marrow aspiration biopsy specimen did not show mastocytosis. The blood serotonin level (SmithKline Bio-Science Laboratories, Van Nuys, Calif) was 2.51 μmol per liter (normal 0.28 to 1.14), and a plasma calcitonin level was 6 ng per liter (normal < 19). Vasoactive intestinal polypeptide and substance P levels (A. I. Vinik, MD, University of Michigan Medical School, Ann Arbor) were undetectable—less than 10 ng per liter and less than 25 ng per liter, respectively. A follow-up abdominal CT scan six months later was unchanged; a chest CT scan with 0.5-cm cuts showed a 6-mm right inferior lung field nodule. Serotonin levels gradually rose, yet urinary 5-HIAA concentrations remained normal. In early 1987, a chest x-ray film showed that the nodule had increased in size to 8 to 9 mm with unchanged findings on an abdominal CT scan. No evidence suggested that the minor abdominal lymphadenopathy (nodes ≤ 1 cm), which had remained unchanged over a two-year period, represented carcinoid metastases. The patient finally consented to wedge resection of the right middle lobe. A localized carcinoid nodule was removed, but postoperatively his flushing persisted.

Intestinal pseudo-obstruction with abdominal pain occurred three months later, and for the first time small liver metastases were noted by CT and magnetic resonance imaging. Angiography showed extensive mesenteric encasement and splenic artery occlusion consistent with an unresectable infiltrative mass lesion deep at the root of the mesentery in the region of the pancreatic head (not visualized by CT or magnetic resonance imaging). Large venous varicosities draining into the caval system were noted in the retroperitoneal area.

Intractable abdominal pain ensued with nonobstructive nausea, vomiting, and weight loss, and the 24-hour urinary concentration of 5-HIAA increased to 345 μmol. Octreotide therapy was begun in August 1987, and the dosage was gradually increased to 200 μg subcutaneously twice a day. Within two months, his abdominal pain decreased considerably, with a reduction in flushing and diarrhea to once or twice a month. As of November 1988, he had gained 8 kg (18 lb) and was free of flushing and abdominal pain with the discontinuation of narcotic analgesia ten months before. Urinary 5-HIAA concentrations fell to 40 μmol per day. A follow-up CT scan showed no growth of liver metastasis; no additional metastases were noted. The only complications of octreotide therapy were mild steatorrhea—16.8 grams per 24 hours (normal < 7.0)—and gallstones noted by sonography after nine months of treatment; both have remained asymptomatic. Interestingly, dysosmia, which was noted by the patient early in his course, diminished markedly during octreotide therapy.

Discussion

The differential diagnosis of flushing is diverse,[5,6] and the clinical evaluation can be challenging. Provocative testing with ethanol, epinephrine, or pentagastrin[2,7-9] can be done to precipitate flushing in doubtful circumstances, but the results are not specific[5] and the test may induce dangerous tachycardia or hypotension. When used in combination with measuring specific markers such as tachykinins, provocative testing may be diagnostic.[9]

If the clinical suspicion warrants, a search for other hormonal markers should be undertaken in a patient with flushing and normal 5-HIAA levels. Blood serotonin is an excellent marker of carcinoid hypersecretion,[6,8,10-12] as shown in this case. Urinary serotonin[10,12,13] and histamine,[2,10] circulating levels of substance P,[9,11,12] chromogranin,[14] neurotensin,[12] and other tachykinins,[9] and platelet serotonin levels[12,13,15] may also have value as carcinoid markers. Selective tumoral production of 5-hydroxytryptophan, particularly by foregut carcinoids, has been reported,[2,16] but levels of urinary 5-HIAA and serotonin are usually abnormal in these patients[13,16] because of a peripheral conversion of 5-hydroxytryptophan to serotonin and 5-HIAA. Less than 1% of carcinoid syndrome patients present with initially normal 5-HIAA levels.[4]

The carcinoid syndrome may occur in the absence of liver metastases if the primary tumor originates from the bronchus[17,18] or ovary[11,19,20]; this is extremely rare in carcinoids of gastrointestinal origin.[21] Although our patient did not display the intense prolonged flushing variant that has been described in some patients with bronchial carcinoids,[22] a thorough evaluation did not reveal evidence of tumor other than the lung nodule before surgical intervention. Carcinoid tumors of the retroperitoneum and pancreas are rarely encountered in large series of carcinoid syndrome patients.[1-4,23] To our knowledge, our patient's presentation with flushing due to an occult retroperitoneal carcinoid is unique.

The long-acting somatostatin analogue octreotide has received recent approval for marketing in the United States for the treatment of the carcinoid syndrome. Several studies have shown excellent response rates to octreotide in such patients, with reductions in flushing, diarrhea, and urinary 5-HIAA levels[4,24,25] and a reversal of the carcinoid crisis.[26] Overt regression of carcinoid tumors with the use of octreotide has been reported but is relatively uncommon.[4,24,25,27]

Our patient manifested a remarkable and sustained decrease in abdominal pain during octreotide therapy. Crampy abdominal pain in the carcinoid syndrome has been attributed to a direct bowel effect of serotonin[28]; more intense pain is usually due to mesenteric retraction or tumor-related fibrosis with or without small bowel obstruction, mesenteric arterial insufficiency, or stretching of the liver capsule by metastatic tumor. Spontaneous necrosis of large liver metastases may present as an acute abdomen. This effect of octreotide therapy in our patient may relate to decreased hormonogenesis or mesenteric tumor shrinkage below the limits of CT detection; alternatively, octreotide may modulate pain as a neurotransmitter in the peripheral or central nervous system.[29] Our results suggest that octreotide therapy should be considered in a patient with carcinoid with notable nonobstructive abdominal pain, even in the absence of troublesome flushing or diarrhea.

Steatorrhea appears to be a dose-related side effect of octreotide therapy[24,30]; it rarely presents a clinical problem other than transiently bulky stools at the time of dosage escalations. Endogenous somatostatin excess is associated with gallstone formation,[31] and gallstones and occasionally overt cholecystitis have been reported in patients treated long term

with octreotide.[4,32,33] We recommend monitoring all patients during long-term octreotide therapy with periodic gallbladder sonography.[33]

A final clinical caveat is our patient's altered olfactory sensation at the onset of carcinoid symptoms with subsequent clear-cut subjective improvement after octreotide therapy. This may represent a new feature of the syndrome related to neurohumoral secretion[34] that has not been reported previously.

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